REMARKS

Claims 25-50, 60-131, and 133-151 will be pending in this application upon entry of the present response.

I. Withdrawn Rejections

The Examiner asserts on page 2, first paragraph of Paper No. 22 that one of skill in the art would find the CRCGCL protein could be used as a marker for T cell activation. Applicants note that use of the claimed polynucleotides is not limited to detection of activated T-cells. Many additional uses for polypeptides of the present invention are disclosed in the specification as filed. As described on page 58, lines 33-36 of the specification, polypeptides of the present invention (which include fragments and variants of SEQ ID NO:2) can be used to stimulate T-cell and B-cell proliferation. Moreover, as mentioned in the specification at page 45, lines 20-26 and page 57, lines 5-7, CRCGCL polypeptides (particularly soluble fragments) can act as antagonists to inhibit T-cell proliferation, differentiation, or chemotaxis. The inhibitory effect of CRCGCL fragments or variants is further supported by the data presented in Paul Moore's Declaration submitted on February 27, 2001. In his Declaration, data is presented showing that a soluble extracellular domain of CRCGCL binds a cytokine and inhibits CRCGCL activity in 293T cells (*see* Declaration section 4). Applicants emphasize that the Declaration of Thi-Sau Migone, submitted on February 8, 2002 supports the above contemplated uses of polypeptides of the present invention. In section 17 of her Declaration, Dr. Migone states:

> An immunologist, after reading these statements made in the 626 Application and based upon what was known in the field of cytokine research, would understand that the 626 Application is directed to the use of the CRCGCL receptor protein as a

> positive regulator of T cell proliferation and would also understand that the CRCGCL receptor protein antagonist is useful for inhibiting T cell proliferation...

Therefore, Applicants respectfully submit that one of skill in the art, as attested to by Dr. Thi-Sau Migone's Declaration, would understand from reading the specification as filed that CRCGCL is useful as a positive regulator of T cell proliferation, and that protein antagonists are useful for inhibiting T cell proliferation.

II. Rejections under 35 U.S.C. §112, first paragraph.

A. On page 3, paragraph 3 of Paper No. 22, claims 25-50, 61-131, and 133-151 stand rejected as allegedly not being enabled in their full scope. Specifically, the Examiner alleges that the specification only enables polynucleotides encoding fragments or variants of SEQ ID NO:2 that can be used "as hybridization probes to detect activation of T-cells" or "to raise antibodies useful for the detection and/or isolation of activated T-cells." The Examiner further states

> Of those polynucleotides that may not be useful as probes, it can be expected that only a small number will encode a polypeptide of SEQ ID NO:2 due to the degeneracy of the genetic code. This small number is enabled. However, polynucleotides encoding variants of SEQ ID NO:2 are not enabled.

Applicants respectfully disagree and traverse.

Preliminarily, Applicants point out that many of the claimed polynucleotides encoding fragments and variants of SEQ ID NO:2 can be used to generate such fragments or variants for use, for example, in generating CRCGCL-specific antibodies or for generating soluble fragments of CRCGCL for use as antagonists. These polynucleotides are not limited

to those that can be used as hybridization probes. Therefore, limiting the claims to those that can only be used as probes is unnecessary.

The specification provides ample guidance for one of ordinary skill in the art to routinely make and use the polypeptides encoded by the claimed polynucleotides of the present invention. The specification discloses routine methods for generating antibodies directed to CRCGCL (see, e.g., pages 27-32; and Example 11), routine methods of identifying antagonists of CRCGCL (see e.g., pages 62-63), and biological assays including, for example, assays to determine if a protein proliferates T-cells (see e.g., pages 88-89, Example 14; pages 92-94, Example 17). Antibodies generated according to methods disclosed in the specification or otherwise known in the art may routinely be applied to determine whether these antibodies immunospecifically bind the polypeptides encoded by the claimed polynucleotides.

Therefore, since the disclosed or otherwise known methods of making and screening polypeptides, and fragments or variants thereof, encoded by the claimed polynucleotides, may be used to make and then determine, without undue experimentation, whether a given polypeptide encoded by a polynucleotide encompassed by the claims is able to, for example, generate antagonists (including, but not limited to, for example, antibodies against CRCGCL and/or soluble fragments of CRCGCL) which would be useful in inhibiting the proliferation, differentiation or chemotaxis of T-cells, and in the treatment of autoimmune disorders, such as leukemia; or generate CRCGCL fragments or variants which could be useful in stimulating T-cell proliferation; and therefore possess the disclosed utility, the enablement requirement is fully satisfied. *In re Wands*, 8 USPQ2d at 1404; *Ex parte Mark*, 12 USPQ2d 1904, 1906-1907 (B.P.A.I. 1989). A patent specification which teaches how to make and use the invention must be taken as enabling unless the Patent Office provides sufficient reason to

doubt the accuracy of the disclosure. *In re Marzocchi*, 439 F.2d. 220, 223-224, 169 U.S.P.Q. 367, 369-370 (C.C.P.A. 1971). The Examiner has not yet provided any evidence to doubt the enablement of the claimed CRCGCL polynucleotides to generate antagonists such as, but not limited to, antibodies against CRCGCL and/or soluble fragments of CRCGCL, or to generate variants that likewise inhibit T-cell proliferation.

In view of the foregoing, Applicants submit that the claims fully meet the enablement requirements of 35 U.S.C. § 112, first paragraph, and respectfully request that the rejection be withdrawn.

B. On page 4, paragraph 4 of Paper No. 22, claims 140-155 directed towards fragments with activity remain rejected under 35 U.S.C. §112 as allegedly not being enabled. Specifically, the Examiner states that, although the claims are directed towards polynucleotides encoding polypeptide fragments that regulate the differentiation and or proliferation of immune cells, "the specification has failed to teach one of skill in the art which cell types to use...to regulate cell differentiation and/or proliferation with CRCGCL." The Examiner further alleges that "the specification has not taught whether to use CRCGCL to promote or to inhibit cell differentiation and/or proliferation" and "the specification asserts that CRCGCL binds to cytokines but does not provide evidence to support the assertion..." Applicants respectfully disagree and traverse.

The specification clearly asserts, for example, on page 56 lines 3-5 that CRCGCL polypeptides may be used to regulate the proliferation, differentiation, or mobilization of immune cells. The specification defines immune cells on page 56, lines 6-8, as

> Immune cells develop through a process called hematopoiesis, producing myeloid (platelets, red blood cells, neutrophils, and macrophages) and lymphoid (B and T lymphocytes) cells from pluripotent stem cells.

On page 56, lines 19-21 it is stated that "CRCGCL polypeptides or polynucleotides could be used to increase differentiation and proliferation of hematopoietic cells" (emphasis added). And finally, on page 58 lines 33-36 the specification reads, "CRCGCL polypeptides or polynucleotides can be used to treat or detect infectious agents. For example, by increasing the immune response, particularly increasing the proliferation and differentiation of B and/or T cells, infectious diseases may be treated" (emphasis added). Thus, CRCGCL polypeptides are clearly asserted to affect the proliferation and differentiation of immune cells, particularly hematopoietic cells, T cells, and B cells. As stated above, the Declaration of Dr. Thi-Sau Migone supports the fact that this cell specificity is clearly indicated in the specification (*see* section 17 of the Declaration).

Applicants also respectfully disagree with the Examiner's allegation that the specification has failed to teach whether to use CRCGCL to promoter or inhibit cell differentiation and/or proliferation. The specification clearly teaches that CRCGCL polynucleotides and polypeptides of the present invention can be used to regulate proliferation and/or differentiation of immune cells, including hematopoietic cells, T cells, and B cells. For example, the specification at page 56 lines 19-21 states that polypeptides of the present invention can be used to "increase differentiation and proliferation of hematopoietic cells, including the pluripotent stem cells", while at page 57, lines 5-8 it is taught that "the administration of CRCGCL polypeptides or polynucleotides that can inhibit an immune response, particularly the proliferation, differentiation, or chemotaxis of T-cells, may be an effective therapy in preventing autoimmune disorders."

Additionally, the Declaration of Dr. Thi-Sau Migone submitted February 8, 2002 states that after reading the specification, one skilled in the art "would understand that the 626 Application is directed to the use of the CRCGCL receptor protein as a positive regulator of T

cell proliferation and would also understand that the CRCGCL receptor protein antagonist is useful for inhibiting T cell proliferation and therefore will be useful to treat certain immune disorders, particularly those related to T cells" (*see* Declaration section 17). Therefore, Applicants respectfully disagree with the Examiner's allegation that the specification has not taught whether to use CRCGCL to promote or to inhibit cell differentiation and/or proliferation, since it is clear to one of skill in the art, as attested to by Dr. Thi-Sau Migone's Declaration, that the CRCGCL receptor protein is involved in stimulating cell differentiation and/or proliferation, while fragments or variants that act as antagonists can inhibit this activity.

Finally, Applicants disagree with the Examiner's allegation that the specification asserts that CRCGCL binds to cytokines but does not provide evidence to support the assertion and therefore, absent evidence to the contrary, CRCGCL (alone) would not be expected to regulate the differentiation and/or proliferation of cells. Preliminarily, Applicants respectfully submit that it is unclear how this particular line of inquiry is relevant to a proper legal analysis of enablement, particularly when the utility rejection under 35 U.S.C. §101 was overcome. The Examiner's assertion above appears to be a credible utility rejection. Second, the MPEP at §2107.02 III at pages 2100-39 to 40 makes quite clear that it is improper to simply dismiss an applicant's assertion of utility as "false" without first asking if there is any reason to question the truth of the statement of utility. The MPEP states that "...if the applicant has presented facts that support the reasoning used in asserting a utility, Office personnel must present countervailing facts and reasoning sufficient to establish that a person of ordinary skill would not believe the applicant's assertion of utility, where the initial evidentiary standard used during evaluation of this question is a preponderance of the evidence (i.e., the totality of facts and reasoning suggest that it is more likely than not that the

statement of the applicant is false" (see MPEP§2107.02 III(A) at page 2100-40, citing In re Brana, 51 F.3d 1560, 34 USPQ2d 1436 (Fed. Cir. 1995)). I

As discussed in Applicant's previous response, the specification discloses that the CRCGCL polypeptide of the present invention demonstrates regions of functional homology with that of IL-2 receptor gamma (*see* Specification page 2, lines 27-31, page 7, lines 25-34, and Figure 2). In addition, tissue expression also indicates a role in immune function, as stated on page 8, line 32 to page 9, line 4 of the spec, and as attested to by Dr. Thi-Sau Migone's Declaration, described above (*see* Section 14 of the Declaration). Therefore, Applicants respectfully submit that one of skill in the art, in reading the present specification, would find it more likely than not true that the claimed invention is a cytokine receptor, which is reflected in paragraphs 16 and 17 of Dr. Thi-Sau Migone's Declaration.

Furthermore, Applicants respectfully point to the Declaration of Paul Moore, submitted on February 27, 2001. In this Declaration, Dr. Moore presents evidence that the CRCGCL receptor does, in fact, bind a cytokine. Flow cytometry was used to measure whether CRCGCL polypeptides bind a cytokine, and the results indicated that 293T cells transfected with a CRCGCL construct bound cytokine (TSLP) versus untransfected 293T cells. Furthermore, additional laboratories have also shown that the CRCGCL receptor, now known in the art as TSLPR, binds the cytokine TSLP (*see* Reche et al., submitted as Exhibit A with response on November 21, 2001). Applicants point out that subsequently-generated data (*e.g.*, Paul Moore's Declaration and Reche et al.) can be used to support the credibility of a utility asserted in the specification, that being that the CRCGCL receptor likely is a cytokine receptor (*see* Specification page 1, lines 8-9 and page 8, lines 32-34). As the Federal Circuit held in *In re Brana*, evidence dated after the filing date "can be used to substantiate any doubts as to the asserted utility since this pertains to the accuracy of a

statement already in the specification." 51 F. 3d. 1560, 1567 at n.19 (Fed. Cir. 1995). Such evidence "goes to prove that the disclosure was in fact enabling when filed (*i.e.*, demonstrated utility)." *Id., citing In re Marzocchi*, 439 F2d. at 224 n.4, 169 U.S.P.Q. at 370 n.4, emphasis added.

Applicants additionally point out that in order to enable the claimed invention as required by 35 U.S.C. §112, the specification need only enable a person of ordinary skill in the art to make the polypeptides encoded by the claimed polynucleotides and practice a single use thereof without undue experimentation. The Examiner states that "undue experimentation would be required of the skilled artisan to use the claimed invention..." (see Paper No. 22, page 6). Applicants respond that since the specification clearly discloses routine methods for generating antibodies directed to CRCGCL (see, e.g., pages 27-32; and Example 11), routine methods of identifying antagonists of CRCGCL (see e.g., pages 62-63), and biological assays including, for example, assays to determine if a protein proliferates T-cells (see e.g., pages 88-89, Example 14; pges 92-94, Example 17), undue experimentation would not be required to use the claimed invention. Undue experimentation is experimentation that would require a level of ingenuity beyond what is expected from one of ordinary skill in the field. *Fields v. Conover*, 170 USPQ 276, 279 (C.C.P.A. 1971). The experiments described in the specification to, for example, identify CRCGCL antagonists, or determine if a protein proliferates T-cells, are routine methods commonly performed by those of ordinary skill in the art, and would not, in any way, qualify as "undue".

In view of the above remarks and amendments, Applicants submit that the claims fully meet the enablement requirements of Section 112, first paragraph, and respectfully request that the rejection be withdrawn.

C. Claims 25-50, 60-131 and 133-155 remain rejected under 35 U.S.C. §112, first paragraph for alleged lack of written description. Specifically, the examiner states

> the claims encompass polynucleotides not described in the specification, e.g., sequences from other species, mutated sequences, allelic variants, or sequences that have a recited degree of identity. None of these sequences meet the written description provision of 35 U.S.C. 112, first paragraph.

Applicants respectfully disagree and traverse.

As stated in Applicant's previous response, it is well established that "[a] gene is a chemical compound, albeit a complex one." *Amgen Inc. v. Chugai Pharmaceutical Co., LTD.*, 927 F.2d 1200, 1206 (Fed. Cir. 1991). Furthermore, as stated by Judge Lourie in *University of California v. Eli Lily*, "In claims involving chemical materials, generic formulae usually indicate with specificity what the generic claims encompass. One skilled in the art can distinguish such a formula from others and can identify many of the species that the claims encompass." Applicants submit that any skilled artisan can readily identify every polynucleotide encoding a polypeptide having the recited % identity of SEQ ID NO:2, and distinguish them from other materials. The Examiner contends that the recitation of "a polypeptide 95% identical to SEQ ID NO:2" does not describe a polypeptide, nor does it describe any particular amino acid sequence. Applicants disagree and submit that the description "95% identical to SEQ ID NO:2" is a clear and precise description of a genus of polypeptides. While it may not offer an exact amino acid sequence of each polypeptide, one of skill in the art could quite readily recognize the polypeptides encoded by the claimed polynucleotides as distinguished from those not claimed (i.e., polypeptides having less than 95% amino acid sequence identity to SEQ ID NO:2). Furthermore, according to the Manual of Patent Examining Procedure, "the subject matter of the claim need not be described

literally (i.e., using the same terms or *in haec verba*) in order for the disclosure to satisfy the written description" (*see* MPEP 2163.02).

For the reasons mentioned above, Applicants respectfully submit that the specification conveys with reasonable clarity that Applicants were in possession of the claimed invention. Accordingly, Applicants respectfully request that the rejection of claims 25-50, 60-131 and 133-155 under 35 U.S.C. §112, first paragraph, for inadequate written description be withdrawn.

II. Rejections under 35 U.S.C. §102

Claims 140, 143, and 153 are rejected under 35 U.S. §102(b) as being anticipated by GenEmbl accession number X91553. This reference discloses a polynucleotide that comprises a nucleic acid that encodes the amino acid phenylalanine. The Examiner states

> It is inherent feature of phenylalanine that it promotes (enhances) the proliferation of all animal cells (immune cells included) because it is an essential amino acid.

Applicants disagree and traverse.

Phenylalanine, along with other amino acids necessary to sustain culture of mammalian cells, is an essential amino acid that supports cell viability and proliferation. However, to say that these essential amino acids enhance cell proliferation is misleading. The essential components of minimal cell culture media allow cell proliferation to occur, i.e., they *support* cell growth. In contrast, cell culture additives that enhance or inhibit cell proliferation are those that can either increase or decrease cell growth significantly above or below the normal amount that occurs under minimal culture conditions (which include the essential amino acids arginine, histidine, isoleucine, leucine, lysine, methionine,

phenylalanine, threonine, tryptophan, valine, cystein, glutamine, and tyrosine, *see* Molecular Cell Biology, Darnell and Lodish, page 192). As stated in Applicant's previous Office Action Response, no reasonable person of skill in the art would equate a protein having "modulating" (inhibiting or enhancing) activity with that of an amino acid having supportive, nutrient properties. When scientists routinely test proteins for their ability to inhibit or enhance activity of different cell types, they measure the effect of their protein of interest on the activity as compared to basal, control levels of activity in a nutritious culture media environment (which includes the essential amino acids listed above). Thus, while phenylalanine is an essential nutrient to support cell growth and viability, it does not "enhance or inhibit" cell growth above or below levels seen in standard culture conditions of which it is a component.

In view of the above comments, Applicants submit that GenEmbl Accession No. X91553 does not anticipate, expressly or inherently, or render obvious the claimed invention. Accordingly, Applicants respectfully request that the rejection of claims 140, 143, and 153 under 35 U.S.C. §102(b) be withdrawn.

CONCLUSION

In view of the foregoing remarks, applicants believe that this application is now in condition for allowance.

If there are any fees due in connection with the filing of this paper, please charge the fees to our Deposit Account No. 08-3425. If a fee is required for an extension of time under 37 C.F.R. §1.136 not accounted for above, such an extension is requested and the fee should also be charged to our Deposit Account.

Respectfully submitted,

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